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ENVIRONMENTAL ASBESTOS EXPOSURE DURING CHILDHOOD AND CANCER RISK LATER IN LIFE

– A LONG-TERM REGISTER-BASED COHORT STUDY

BY
SOFIE BÜNEMANN DALSGAARD

DISSERTATION SUBMITTED 2019

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DENMARK

Environmental Asbestos Exposure During Childhood and Cancer Risk Later in Life – A Long-term Register-based Cohort Study

PhD dissertation

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PREFACE

This dissertation presents the work carried out during my employment in the period from 2016 to 2018 at Aalborg University where I worked at the Department of Occupational and Environmental Medicine, Aalborg University Hospital.

I would like to thank all my suprvisors Else Toft Würtz, Oluf Dimitri Røe, Johnni Hansen, and Øyvind Omland for their help and guidance and for generously sharing with me their knowledge and expertise within their espective scientific fields. A special thanks to Øyvind Omland who came up with the idea for and initited the present project, and to Johnni Hansen who prepared all the data and constructed the job exposure matrix.

I am especially grateful to Else Toft Würtz who has been my closest sparring partner. Thank you for all your assistance, support and discussions – and not least, thank you for your patience! I could not have done it without you.

At the Department of Occupational and Environmental Medicine, I would like to thank all my colleagues; you made me feel ‘at home’ from day one.

Finally, I wish to thank my family, especially Morten,who always believes in me and has supported me all the way.

Sofie Bünemann Dalsgaard
February 2019

THE DISSERTATION IS BASED ON THE FOLLOWING PAPERS

Paper I: Environmetal asbestos exposure in childhood and risk of mesothelioma later in life: a long-term follow-up register-based cohort study [Accepted for publication in Occup Environ Med]
Dalsgaard SB, Würtz ET, Hansen J, Røe OD, Omland Ø.

Paper II: Cancer incidence and risk of multiple cancers after environmental asbestos exposure in childhood - a long-term register-based cohort study [Manuscript]
Dalsgaard SB, Würtz ET, Hansen J, Røe OD, Omland Ø.

Paper III: A cohort study on cancer incidence among women exposed to environmental asbestos in childhood with focus on female cancers including breast cancer [Manuscript]
Dalsgaard SB, Würtz ET, Hansen J, Røe OD, Omland Ø.

ABBREVIATIONS

ATP	The Danish Supplementary Pension Fund Registry
CI	Confidence interval
CPD	Chronic obstructive pulmonary disease
CRS	The Danish Civil Registration System
DCR	The Danish Cancer Registry
DLCR	The Danish Lung Cancer Registry
DSE77	The Danish version of the International Standard Industrial Classification of All Economic Activities
E	Expected number of cases
HR	Hazard Ratio
ISIC-6	International Standard Industrial Classification of All Economic Activities from 1968
IARC	International Agency for Research on Cancer
JEM	Job exposure matrix
MM	Malignant mesothelioma
NOA	Natural occurring asbestos
NOCCA	Nordic Occupational Cancer Study
NPR	The Danish National Patient Registry
O	Observed number of cases
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio

CONTENTS

1. INTRODUCTION

It is well documented that asbestos exposure is associated with certain cancers[1]. An asbestos ban has therefore been introduced in many countries. However, asbesto is still being used in several countries around the world[2]. Before the asbestos ban in Denmark in the 1980s, Denmark was a big consumer of asbestos. The asbestos-cement factory operating in the city of Aalborg in northern Denmark in the period from 1928 to 1986 was the largest Danish consumer of asbestos[3]. The factory was located in the center of Aalborg surrounded by residential quarters, schools, and businesses.

Asbestos exposure is associated with mesothelioma in particular[1]. Due to the long latency between asbestos exposure and development of malignant mesothelioma, the incidence of malignant mesothelioma continues to increase[4]. In Denmark, the incidence of malignant mesothelioma rose from 2.5 to 4.9 per 100,000 person-years in the period frm 1990 to 2015[5].

The majority of previous asbestos studies have focused on asbestos exposure in occupational settings. Only few studies have addressed potential consequences of environmental asbestos exposure during childhood. In the present study, we use Danish registries and an edited and supplemented version of the Nordic Job Exposure Matrix to differentiate between occupational, familial, and environmental asbestos exposure while examining the risk of cancer after environmental neighborhood asbestos exposure in childhood.

2. HYPOTHESIS AND AIMS

We hypothesized that environmental asbestos exposure in childhood increases the risk of cancer later in life.

Three studies were undertaken with the following aims:

Study I: To examine the risk of developing malignant mesothelioma after environmental neighborhood asbestos exposure in childhood.

Study II: To investigate the risk of all types of cancer in general and asbestos-associated cancers in particular as well as the risk of developing more than one cancer after environmental asbestos exposure in childhood.

Study III: To study the risk of all types of cancer with a focus on female cancers including breast cancer after environmental asbestos exposure in childhood.

3. BACKGROUND

3.1 Asbestos

Asbestos is a group of naturally occurring mineral silicate fibers. Asbestos can be divided into two mineralogical groups; the amphiboles with long, straight fibers (crocidolite, amosite, tremolite, anthophyllite, and actinolite) and the serpentines, which solely consist of chrysotile with characteristic short, curly fibers[6]. Asbesto has been called the “magic mineral” because asbestos fibers are resistant to heat, fire and chemicals, and do not conduct electricity[7]. Because of these properties, asbestos has been widely used in many different products ranging from construction materials for house and shipbuilding to insulation of water and combustion pipes. Asbestos has even been used to make toys for children[8].

The use of asbestos began about 4,500 years ago. The modern asbestos industry started as textile manufacturing in the early 1800s in Italy[9]. In Denmark, the production of asbestos-cement began in 1928 at the asbestos factory, Danish Eterit, in Aalborg. About 90% of the imported raw asbestos in Denmark was used in the production of asbestos-cement products up until 1984, and a total of approximately 620,000 tons of asbestos were consumed[3]. Figure 1, from the dissertation by Edith Raffn, shows the annual consumption of asbestos by fiber type used in the production of asbestos-cement products; 89% chrysotile, 10% amosite, and 1% crocidolite[3].

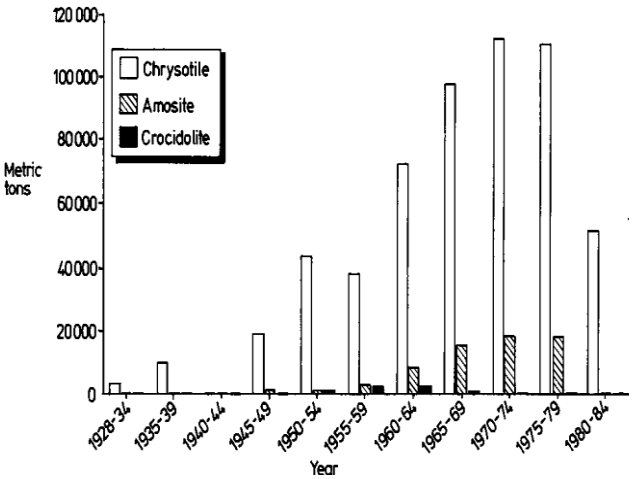

Figure 1. Annual consumption of asbestos by fiber type in the period 1928-1984[3]

3.2. Environmental asbestos exposure

In this section, the various groups of environmental asbetos exposure will be listed and briefly explained.

Environmental exposure from industrial operations

Asbestos exposure from industrial operations potentially occurs via airborne emission during loading and unloading of asbestos, in processing, or through ventilation or waste disposal activities[10]. This type of environmental asbestos exposure is often termed neighborhood or residential asbestos exposure and is the main focus of our studies. Previous studies have suggested that that production facilities using asbestos contaminate their neighborhoods[11-13]. However, not all studies have found an association between malignant mesothelioma (MM), the cancer most strongly associated with asbestos, and residential asbestos exposure[11,14].

Familial occupational asbestos exposure

Familial ocupational asbestos exposure refers to asbestos exposure brought home by a person exposed to occupational asbestos. The most common activity attributed to familial occupational asbestos exposure is laundering of contaminated clothes from asbestos workers[10]. Several studies have pointed to an increased risk of disease associated with take-home exposures to asbestos fibers from asbestos workers' cothing[15-17].

Other terms for familial occupational asbestos exposure and take-home exposure include para-occupational exposure, household exposure and domestic exposure. In our study, we have termed such exposure "familial asbestos exposure" (Study I) and "relatives' occupational asbestos expsure" (Study II+III).

Exposure to asbestos-containing products

Despite the asbestos ban, many asbestos-containing products still exist as they are fixed in structures like roofing, asbestos-cement products, and insulation, among others. In Denmark, existing asbestos-containing products are legal to use if they have been installed before January 2005[18]. Assessing exposure from use of asbestos-containing products is difficult; indeed impossible in our register-based study.

Naturally occurring asbestos

Naturally occurring asbestos (NOA) includes the asbestos-like fibrous minerals that occur naturally in rocks and soils. NOA has been found among other in areas in Turkey, Italy, and Nevada[19-21]. In Denmark, NOA does not exist.

Environmental asbestos expsure in children
Historically, children have been exposed to asbestos when living near asbestos mines or asbestos industries using asbestos-containing materials or living with asbestos workers. Neighborhood asbestos exposure in childhood was first recognized by Wagner et al in 1960[22]. Anderson et al. reported characteristic radiologic changes and female pleural mesothelioma cases after childhood exposure from living with workers employed in a factory producing amosite asbestos products[23]. Furthermore, other case reports concerning asbestos exposure in childhood have been described [24-26].

Environmental asbestos exposure near the asbestos-cment factory in Aalborg
To our knowledge, no dust count measurements have been performed outside the asbestos-cement factory in Aalborg. Therefore, we have no quantitative data on the degree of asbestos contamination of the air outside the asbestos factory. Based on measurements from the asbestos-cement factory in 1948 and 1957, the Danish national Institute of Ocupational Health estimated that the concentration varied between 50 and 800 fibers per milliliter (f/ml) in 1948 and between 10 and 100 f/ml in 1957[27]. The measurements from 1948 indicated that fiber levels may have ranged 100-1600 times above the Danish threshold limit value of 05 fiber/ml[28]. In light of the high levels of airborne asbestos at the factory together with reports from people living in Aalborg in the asbestos-cement production period having experienced asbestos dust in the surroundings of the factory (personal communication), we assume that asbestos pollution from the factory to the neighborhood has been substantial.

3.3 Asbestos ban in Denmark
The asbestos ban in Denmak did not happen at once. In 1972, the use of asbestos for thermal and noise insulation and waterproofing was banned[29]. Eight years later, in 1980, all use of asbestos was banned with an exemption for use of asbestos in brake blocks and asbestos-cement roofing[29,30]. In 1986, the Danish parliament passed further restrictions, and all poduction of asbestos-containing fiber cement stopped in 1988[3].

3.4 Asbestos-induced pathogenesis

The pathologic effects of asbestos are associated with the type of mineral, the dimension and concentration of fibers, as well as the duration of exposure[31]. The following hypotheses regarding asbestos-induced carcinogenicity have been proposed:

- The “oxidative stress theory” hypothesizes that phagocytic cells are unable to digest elongated fibrs and generate free radicals leading to DNA damage and genomic instability resulting in carcinogenic transformation[6,32].
- The “chromosome tangling theory” suggests that asbestos fibers damage chromosomes during cell division[6].
- In laboratory animals, asbestos fibers have been shown to induce macrophage activation and release cytokines and growth factors leading to persistent inflammation and tumor promotion[1].

3.5 Asbestos and cancer risk

The International Agency for Research on Cancer (IARC) has concluded that exposure to asbestos is associated with an increased risk of MM and cancer of the lung, larynx, and ovary. In addition, positive associations have been established between asbestos exposure and cancer of the pharynx, stomach, and colorectum[1].

It has been debated whether shorter fibers (chrysotile) are less carcinogenic than longer fibers (amphibole)[33]. However, according to the IARC, the current international perception is that all forms of asbestos are classified as group I carcinogens to humans[1].

Malignant mesothelioma

Scientific evidence associating asbests exposure with cancerous disease was presented in 1960 when Wagner et al. found probable asbestos exposure in 32 of 33 MM cases[22]. Numerous studies have confirmed the association between occupational asbestos exposure and the development of MM, including Raffn et al. who found that the excess risk of MM in pleura of male workers employed in the asbestos-cement factory in Aalborg was 5.46 (95% CI 2.62-1.05)[28].

Examining the impact of an asbestos-cement factory on the incidence of mesothelioma by assessing the effects of occupational, familial, and environmental asbestos exposure, Mensi et al. reported an excess of 130 MM cases during a 12-year period[34]. Almost half of these cases were attributable to environmental asbestos exposure[34]. An excess of MM after exposure to

environmental asbestos has also been reported in several other studies[12,35-38].

No other connection between mesothelioma and other exposures, beside asbestos, has been scientifically proven, and no evidence of a threshold level below which there is no risk of mesothelioma has been found[39,40].

Latency period for malignantmesothelioma

The latency period, here defined as the time between the first asbestos exposure and MM diagnosis, shows a large variability. Latency periods ranged from 14 to 72 years in a study by Bianchi et al.[41]. It has been debated whether there is an inverse relationship between the intensity of asbestos exposure and the length of the latency period; whether lower exposure levels and short durations of exposure to asbestos can lead to longer latency periods. An Italian study examined 2,544 MM cases and their asbestos exposure history. The authors found a median latency period of 44.6 years. It was concluded that anatomical site, gender, and morphology were not relevant for MM latency. However, a shorter latency period was documented among those exposed to occupational asbestos exposure (43 years) than among those exposed to environmental and household asbestos exposure (48 years)[4]. In a cohort of British asbestos workers, Frost et al. did not find sufficient evidence to either confirm the association between latency period and occupation or conclude that greater intensity asbestos exposure led to shorter latency periods[42].

Lung cancer

Doll et al. were the first to demonstrate an excess of lung cancer after occupational asbestos exposure in textile workers ($P<0.00001$)[43]. Male workers employed at the asbestos-cement factory in Aalborg were also found to have an increased risk of lung cancer (standardized incidence ratio (SIR) 1.7, 95% confidence interval (CI) 1.5-2.0) [27]. As for the association between environmental asbestos exposure and lung cancer, Mzileni et al. observed a positive association between lung cancer and residential asbestos exposure from living in a crocidolite and amosite mining area in the Northern Province of South Africa[44]. The highest risk of lung cancer was seen among female residents of heavily polluted asbestos areas (OR 5.4, 95% CI 1.3-22.5)[44]. However, in a lung cancer mortality study, the lung cancer risk among women in two chrysotile mining regions of Quebec was not increased compared with women from other areas of Canada (standardized mortality ratio (SMR) 0.99, 95% CI 0.78-1.25).

Larynx cancer

In a review and meta-analysis, Peng et al. confirmed the association of exposure with asbestos, reporting an increased risk of dying from laryngeal cancer among male workers (SMR 1.69, 95% CI 1.45-1.97)[45]. Raffn et al. found that workers employed at the asbestos-cement factory in Aalborg in the period 1928-1940 had an increased risk of laryngeal cancer (SIR 5.50 (95% CI 1.77-12.82), while the overall SIR for cancer of the larynx was not significantly increased (SIR 1.66, 95% CI 0.91-2.78)[28].

Ovarian cancer

In a cohort of wives of asbestos workers in Casale Monferrato, Italy, an "eternit factory" city similar to Aalborg, a statistically non-significant increase in the number of deaths from ovarian cancer was observed[46].

Pukkala et al. examined the incidence of ovarian cancer among women employed in various occupations in the Nordic countries. In some of the groups examined, a statistically significant incidence ratio was observed; e.g. in textile workers, a total of 2,216 ovarian cancers were observed with a SIR of 1.09 (95% CI 1.05-1.14)[47]. Reid et al. conducted a meta-analysis to examine if exposure to asbestos caused ovarian cancer, concluding that women thought to have ovarian cancer had an increased SMR if they reported having been exposed to asbestos compared with reference populations. However, Reid et al. pointed out that some studies could contain errors in classification of the disease[48].

Pharyngeal cancer

In a meta-analysis of published cohort studies examining the association between asbestos exposure and cancer of the pharynx, the Committee on Asbestos from the Institute of Medicine (US) estimated that the aggregated relative risk of pharyngeal cancers for any exposure to asbestos was 1.44 (95% CI 1.04-2.00)[49]. Furthermore, no indication was found that more extreme exposures were associated with a higher risk of pharyngeal cancer[49]. It was concluded that "evidence is suggestive but not sufficient to infer a causal relationship between asbestos exposure and pharyngeal cancer"[49]. The incidence of pharyngeal cancer in the male workers at the asbestos-cement plant in Aalborg was not significantly increased (SIR 0.79, 95% CI 0.42-1.35)[28].

Stomach cancer

Raffn et al. observed an excess number of deaths from cancer of the stomach (SMR 1.43, 95% CI 1.03-1.93) in a cohort of men employed at the asbestos-cement factory in Aalborg[28]. This is in line with the results from a meta-analysis, where the overall meta-SMR for stomach cancer for the total cohort was 1.15 (95% CI 1.03-1.27), though, with heterogeneous results across studies[50].

Colorectal cancer

In the total cohort of asbestos-cement workers in Aalborg, Raffn et al reported an SIR of 1.23 (95% CI 1.01-1.48)[51]. This is in line with the results from a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the colorectum, where the overall relative risk was 1.15 (95% CI 1.01-1.31)[49].

4. MATERIALS AND METHODS

4.1 Danish registers

Five Danish registers were used in this dissertation; the Danish Civil Registration System (CRS)[52], the Danish Cancer Registry (DCR)[53], the Danish Supplementary Pension Fund Registry (ATP)[54], the Danish Lung Cancer Registry (DLCR)[55], and the Danish National Patient Registry (NPR)[56]. Table 1 offers an overview of these data sources and the contents used in the three studies.

Table 1. Summary of Danish registers, used contents, and time span of used contents.

Register	Start year	Study	Used contents	Time span of used contents
The Danish Civil Registration System (CRS)[52]	1968	I, II, III	Civil registration number, sex, date of birth, parish of birth, civil status, relatives (parents, children, and spouse) civil registration number, dates of vital status, emigration, and disappearance	1940*-2015
The Danish Cancer Registry (DCR)[53]	1943	I, II, III	Danish Cancer Society diagnosis codes, diagnosis codes (ICD-7 and ICD-10), date of diagnosis	1968-2015
The Danish Supplementary Pension Fund Registry (ATP)[54]	1964	I, II, III	DSE77 code, date of first workday in an occupation, date of last workday in an occupation, company name, employment period, birth year	1964-2015
The Danish Lung Cancer Registry (DLCR)[55]	2000	II	Smoking status	2000-2015
The Danish National Patient Registry (NPR)[57]	1977	III	Diagnosis codes	1977-2015

* The CRS includes information for persons born before 1968, e.g. parish of birth.

4.2 Study design & ethics

We conducted three retrospective register-based cohort studies using data from the Danish registers summarized in Table 1 together with an evaluated, edited, and supplemented version of the asbestos job exposure matrix from the Nordic Occupational Cancer Study (NOCCA)[58]. Since 2 April 1968, all persons with a permanent residence in Denmark have been assigned a unique 10-digit personal identification number (CPR number)[52]. Using the CPR number, we linked register-based data from the registries at an individual level[52].

All three studies have been performed in accordance with the Helsinki Declaration and approved by the Danish Data Protection Agency (j. no.: 2016-41-4787).

4.3 Study population

From the Aalborg City Archives, we retrieved 7th grade school records on former pupils born 1940-1970 from four schools located near the asbestos-cement factory in Aalborg. We identified all former pupils using their CPR number. The pupils were identified by name and birthplace if no CPR number was available. We excluded school records of pupils who could not be identified or pupils whose CPR number could not be validated in the CRS, or if they were born before 1940 or after 1970, or had multiple records.

From the CRS, we sampled a frequency-matched reference cohort, matched 1:9 on sex and five-year age intervals. A subject in the reference cohort was excluded if registered as a former pupil in the school cohort. We also excluded subjects who had emigrated, died, or been diagnosed with cancer before school start in the year they turned 12.

The flowchart in Paper I describes the establishment of Aalborg School Cohort used in Paper I and II. The study population in Paper III consisted of the females from the Aalborg School Cohort and the corresponding reference cohort.

4.4 Follow-up

In all three studies, the follow-up period began at the earliest on 2 April 1968 (start of the CRS) or on the date of 7th grade school start (1 August).

In Study I and Study II, follow-up ended on the date of diagnosis of the first primary cancer in question, date of death, emigration or disappearance, or 31 December 2015, whichever came first.

In Study III, follow-up ended on the date of death, emigration, or 31 December 2015; all primary cancers were included.

4.5 Environmental asbestos exposure

We assume from the results from previous studies together with historical tellings from people living in the Aalborg area at the time of asbestos-cement production that people living near the asbestos-cement factory have been exposed to environmental asbestos.

The one and only asbestos-cement factory in Denmark (Dansk Eternit Fabrik A/S) was located in the center of Aalborg city. The prevailing wind direction at the location of the factory is west-south-west (Figure 1) [59]. Near the asbestos-cement factory, in the prevailing wind direction, four schools were located: Alléskolen (School A) 100 meters north-east, Sønderbroskolen (School B) 250 meters north, Vejgaard Vestre Skole (School C) 750 meters north-east, and Østermarkens Skole (School D) 750 meters north-east (Figure 2).

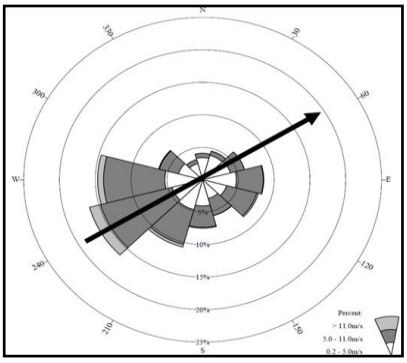

Figure 1. Windrose showing the prevailing wind direction in Aalborg[59].

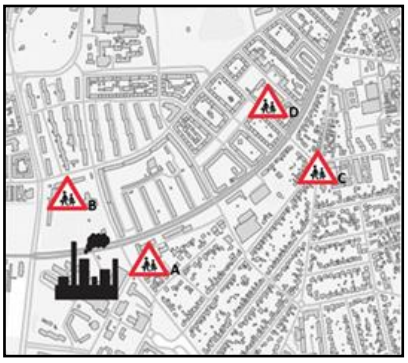

Figure 2. Figure from Paper I showing the location of the four schools in relation to the asbestos-cement factory.

The CRS does not contain complete information on the full address (municipality, road, and house number) of registered citizens until as of 1977[52]. Therefore, we used school attendance close to the asbestos-cement factory as a proxy for living near the factory. This assumption was made because in Denmark, education for 0-9 grades was compulsory; and until 2005, children were assigned to the school nearest their place of residence[60].

The former school children might have been exposed to environmental asbestos exposure for a longer period if they had been living near the asbestos-cement factory before or after their 7th grade. In a sub-analysis, we investigated how many former school children were born in a parish near the asbestos factory. In a radius of 3 kilometers from the location of the asbestos-cement factory, the following twelve parishes are located: Budolfi, Ansgars,

Vor Frelsers, Vor Frue, Sankt Markus, Søndertranders, Nørretranders Vejgård, Hans Egedes, Hasseris, Nørresundby, and Margrethe parish (Figure 3)[61].

Figure 3. Birth parishes near the asbestos-cement factory in Aalborg[61].

We assume that children registered with a birth parish near the asbestos-cement factory have been exposed to environmental asbestos for a longer period than that captured through their primary school attendance. In the Results section, we perform an additional sensitivity analysis restricting the school cohort to those born in a parish near the factory and the reference cohort to those not born in parish near the factory.

A subject from the school cohort was defined as being exposed to environmental asbestos in the absence of both occupational asbestos exposure and relatives' occupational asbestos exposure.

4.6 Assessment of occupational asbestos exposure

To assess occupational asbestos exposure, we used an evaluated, edited, and supplemented version of the Job Exposure Matrix (JEM) from the NOCCA (NOCCA JEM) covering occupational asbestos exposure[58]. The original data from the NOCCA JEM may not be used in secondary publications; however, in this section, it will briefly be described how these data were altered for the present study, and how the data were used.

Structure of the NOCCA JEM

The construction of job exposure matrices for the NOCCA has been described by Kauppinen et al.[58]. The original Danish NOCCA JEM was constructed based of the Finnish JEM by the Danish national expert Johnni Hansen, who served as one of the supervisors of this dissertation[58].

The structure of the NOCCA JEMs is three-dimensional: occupations, agents, and four periods (1945-1959, 1960-1974, 1975-1984, and 1985-1994). Occupational exposure is characterized in terms of proportion of exposed employees within a particular occupation and their mean level of exposure. The criterion for inclusion in the JEM is a minimum level of exposure, usually occupational inhalatory exposure at a level exceeding the background level originating from non-occupational exposure. If the proportion of employees exposed to asbestos within an occupation was below 5% during all periods, it was not included[58].

Translation of Finnish occupational codes into Danish industry codes

We evaluated the Finnish occupational codes (O-codes) from the NOCCA and compared them with codes classified by the DSE77, a Danish version of the ISIC-68 (the International Standard Industrial Classification of All Economic Activities). For some occupations, there was no translation for a corresponding DSE77 code, for example O-code 651 ,“Fitter-assemblers etc.” Such occupations were therefore omitted. For some of the translated DSE77 codes, we assessed the proportion of asbestos exposed to be below 5% during all periods; for example DSE77 95190, “Other repair enterprises” translated from O-code 775, “Machine setter operators (not in textile industry) and riggers”. These were omitted as well.

On the other hand, in the overview of old (DB93) and new (DSE77) Danish occupational codes, we observed occupations that were not present in the O-code translation. These codes were added and given the same level of asbestos exposure as comparable translated occupations. For example, both DSE77 71162, “Rescue squads”, and DSE77 91032, “Marine”, were added and given the same proportion of exposed employees as DSE77 71163, “Fire

brigade", and DSE77 71110, "Railroads", which were the corresponding DSE77 codes translated from O-code 530, "Railway engine and lorry drivers, steam engine firemen".

Supplementary Document 12.2 is a final list of the Danish industries with potential asbestos exposure.

Evaluation of local asbestos risk companies
Two specialists in occupational health (Øyvind Omland and Jens Peter Johansen) with thorough historical knowledge of asbestos-consuming companies in Denmark participated in the translation of codes and evaluation of industries, and identified two risk companies; Dansk Eternit Fabrik (the asbestos-cement factory) and Sækkelejekompagniet (company recycling hessian bags).

Proportion of asbestos-exposed subjects within an occupation
In a previous study, it was estimated that approximately 150,000 persons in Denmark had been exposed to occupational asbestos exposure before the asbestos ban in 1986, corresponding to approximately 10% of the working population[62]. With the proportion of asbestos-exposed subjects within an occupation set to 50%, 9.99% of the reference cohort was categorized as exposed to occupational asbestos. In case a DSE77 code was translated to represent different proportions of asbestos exposure, the lowest proportion was used in the definition of an asbestos occupation.

Definition of occupational asbestos exposed subjects
Employment history was extracted from the ATP. Since 1 April 1964, all employees in Denmark have been compulsory members of the ATP, and information on all employments (company codes and DSE77 industry codes), including start and end dates, has been registered and kept for wage earners aged 16-66 years working minimum 9 hours/week[54].
A subject was defined as ever exposed to occupational asbestos if the proportion of asbestos-exposed subjects within an occupation exceeded 50% in at least one job in the period from April 1964 until the end of December 1994.

Relatives' occupational asbestos exposure
Subjects were defined as being subject to relatives' occupational asbestos exposure if we could reasonably assume that the subject was living with a relative working in an asbestos occupation. Relatives (mother, father, siblings, spouses, and children) were identified by the unique identification number in

the CRS. The assessment of relatives' occupational asbestos exposure was similar to the subjects' own occupational asbestos exposure, as described above. In Denmark, the age of attaining legal adulthood is 18 years. In defining if a subject had been subject to relatives' occupational asbestos exposure, legal adulthood was used as the expected date for moving away from parents' home and the earliest date for marriage. A subject was defined as subject to relatives' occupational asbestos exposure if exposure happened to:

- Mother and/or father: in the period from the subject was born (the earliest April 1964, the start of the ATP) to the 18th birthday.
- Siblings: when the cohortee was below the age of 18 years.
- Spouse: when the cohortee was above the age of 18 years.
- Children: when below the age of 18 years.

4.7 Outcome classification

From the DCR, we identified cancer cases registered in the period from April 1968 (start of CRS) to the end of 2015, including tumor characteristics[53]. For the analyses, we used classification codes of the Danish Cancer Society, which holds records of all incidences malignant neoplasms registered since 1943 classified according to an extended Danish version of the ICD-7 (1943-1977), the ICD-O (1978-2003), and the ICD-10 (2004 and onwards) [53]. For example, the Danish Cancer Society code for MM is "61 mesothelioma" and covers validated ICD-10 codes for mesothelioma with location in pleura, peritoneum, and pericardium. Hereinafter, when we refer to "lung cancer", it collectively encompasses cancer of the lung, bronchus, and trachea and "ovarian cancer" encompasses cancer of the ovary, fallopian tube and broad ligament. Cancer diagnoses in the DCR are considered valid, and information bias is assumed not to be present[53].

4.8 Tobacco smoking

Tobacco smoking is a major risk factor for several cancer types and by far the leading risk factor for lung cancer; approximately 75% of all lung cancer deaths are attributable to smoking[63,64]. Furthermore, interaction between asbestos exposure and tobacco smoking causes an additive to multiplicative synergism for lung cancer[65,66]. There is no evidence that MM is associated with tobacco smoking[67]. In the Danish registries, information on smoking is usually not well-recorded[68]. We used two different approaches in an attempt to compensate for the lack of smoking status data.

The Danish Lung Cancer Registry (DLCR)

The DLCR, used in Paper II, contains information on patient characteristics including dichotomized smoking data (ever/never smoker)[55]. The DLCR is not complete, and smoking data were available only for 69.1% of the lung cancer cases from the school cohort and 66.6% of the lung cancer cases from the reference cohort. However, all lung cancer cases from both cohorts in the DLCR were registered as current or former smokers, which supports the risk factor status of smoking.

The diagnosis of COPD as a proxy for current or former smoking

Since cigarette smoking is the most important causative factor for development of chronic obstructive pulmonary disease (COPD), we used the diagnosis of COPD as a proxy for a substantial smoking history (Paper III)[69]. From the NPR, we retrieved information on subjects with the ICD-10 diagnosis code of COPD (J44). All subjects with a diagnosis of COPD were categorized as "smokers".

4.9 Statistics

Statistical analyses were performed using Stata 15.1 (Stata Corp LLC, College Station, Texas, USA).

To compare the categorical variables in the school cohort and the reference cohort, we used the chi-square test. The Wilcoxon-Mann-Whitney test was used to analyze age medians. Subjects without an ATP record were treated as if they had not been exposed to occupational asbestos. For each person, person-years at risk were calculated according to the follow-up period and split into 5-year age and calendar time intervals.

Hazard ratios

The association between environmental asbestos exposure and cancer was analyzed using Cox proportional hazards model (Study I and III). Adjustments were made for the subject's own occupational asbestos exposure (Study I+III), familial occupational asbestos exposure (Study I+III), and smoking (Study III). In Study III, adjustments were performed only if the number of subjects in one of the confounder subgroups exceeded five subjects. In Study I, we used likelihood-ratio test to examine interactions between own occupational and familial asbestos exposure.

Standard incidence ratios (SIRs)

In all three studies, we estimated SIRs with corresponding 95% CIs as the overall number of observed number of cases in the school cohort and the

expected number of cases in the reference cohort. In Study II, the SIR analysis was stratified on asbestos exposure, grouped into four groups: “environmental asbestos exposure”, “relatives’ occupational asbestos exposure”, “occupational asbestos exposure”, and “occupational and relatives’ occupational asbestos exposure”. In Study I, lag time analyses were performed, deferring start of follow-up 10, 20 and 30 years.

Supplementary analyses in Study I

Test for trend was done using school distance as an ordinal variable. The trend analysis did not include subjects who attended more than one school. We performed regression analyses excluding subjects born prior to year 1948, subjects not born in Denmark, and subjects born after 1955 prior to analysis. Furthermore, we performed a sensitivity analysis, recoding subjects without an ATP record as having occupational asbestos exposure. We also performed sensitivity analyses using different cut-points (0%, 10%, 25%, and 75%) for exposure prevalence for categorizing a subject as exposed to occupational asbestos. Finally, we performed an additional analysis, restricting the school cohort to subjects born in a parish near the asbestos-cement factory.

5. Results

The following section summarizes the main results of each study (I-III) and additional results that have not been presented in the appended papers.

5.1 Study I

Mesothelioma risk

A total of 38 MM cases were registered (32 males and 6 females) in the school cohort during the follow-up period. The same number of cases was found in the comparison cohort with 31 male and 7 female cases. This corresponds to an SIR of 8.77 (95% CI 6.38-12.05). Adjusted for occupational asbestos exposure and familial occupational asbestos exposure, the HR for males was 7.01 (95% CI 4.24-11.57); the unadjusted HR for females was 7.43 (95% CI 2.50-22.13).

School distance and mesothelioma risk

No significant trend between school distance and risk of MM was found (p=0.347). The highest HR for MM was found for those who attended the school at about 250 m north of the plant: HR 10.65 (95% CI 5.82-19.48).

Characteristics of asbestos exposure in cases

In total 11 cases from the school cohort (male/female ratio 1.2:1) had no other known asbestos-assessed exposure than the environmental one. Using our JEM, we found that 23 males from the school cohort and 15 from the comparison cohort had been exposed to occupational asbestos. No female cases from either cohort had been exposed to occupational asbestos. The mean cumulated time of employment with potential asbestos exposure was 7.1 years (range 0.1-35.1) for the school cohort and 8.3 years (range 0.1-42.2) for the comparison cohort. The majority of those exposed to occupational asbestos had worked in iron shipyards. Three persons (two from school cohort and one from the comparison cohort) had worked in the asbestos-cement plant in Aalborg.

Age at diagnosis

The median age at diagnosis was 61.0 years (range 39.9-74.4) in the school cohort and 60.2 years (range 42.5-73.0) in the comparison cohort; i.e. there was no significant difference between the two cohorts (p=0.819). Furthermore, in the school cohort, no significant difference was found in median age at diagnosis between those only exposed to environmental asbestos and those

also exposed to occupational asbestos. In a lag time analysis deferring start of follow-up 10, 20, and 30 years, the majority of cases (97%) were found to have developed MM more than 30 years after their 7th grade school attendance.

Additional analysis
In an additional sensitivity analysis, we restricted the school cohort to subjects born in one of the 12 parishes within a 3,000-meter radius from the asbestos-cement factory (75.3%) and the comparison cohort to subjects not born in one of the parishes (98.3%). With this restricted cohort, the hazard ratio adjusted for occupational asbestos exposure and relatives' occupational asbestos exposure was 5.99 (95% CI 3.59-10.01).

5.2 Study II

Cancer incidence ratios
For the school cohort, the incidence was significantly increased both for 'all cancer types' (SIR 1.07, 95% CI 1.02-1.12) and for 'asbestos-associated cancers' (SIR 1.14, 95% CI 1.05-1.24) compared with the reference cohort. Excluding MM cases, i.e. the cancer type with the highest SIR (SIR 8.77, 95% CI 6.38-12.05), we found that the overall cancer incidence was marginally but significantly increased (SIR 1.05, 95% CI 1.00-1.10). However, SIR for all the asbestos-associated cancers fell short of significance when MM cases were excluded (SIR 1.07, 95% CI 0.99-1.17). The risk of developing more than one cancer was not higher in the school cohort than in the reference cohort. Finally, in a sub-analysis, the incidence of asbestos- and tobacco-associated cancers (colon, larynx, lung, pharynx, rectum, and stomach) was significantly increased compared with the reference cohort (SIR 1.11, 95% CI 1.02-1.21).

Cancer incidence rates related to type of exposure
In the subgroup of school children exposed to both environmental and occupational asbestos, the SIRs for 'all cancers' (SIR 1.18, 95% CI 1.06-1.31), 'all asbestos-associated cancers' (SIR 1.47, 95% CI 1.25-1.74), and lung cancer (SIR 1.34, 95% CI 1.05-1.72) were significantly increased. After extracting MM from 'all cancers' and 'all asbestos-associated cancers', the SIR remained significant only in the group of asbestos-associated cancers (SIR 1.30, 95% CI 1.09-1.55). The SIR for MM was significantly increased in all combinations of asbestos exposure, also in those exposed only to environmental asbestos (SIR 5.09, 95% 2.82-9.20). In the subgroup of environmental combined with occupational and relatives' asbestos exposure,

the incidence of pharyngeal cancer was significantly increased (SIR 4.24, 95% CI 1.59-11.29).

Additional analyses
We performed the analyses shown in Table 1-2 separately for males and females (Supplementary document 12.3 and 12.4). In both cohorts, more males than females had been exposed to occupational asbestos, while in both cohorts more females than men had been exposed to occupational asbestos via relatives. When the SIR analyses were separated in gender, it was revealed that only males had a significantly increased overall incidence of 'all cancer types' (SIR 1.17, 95% CI 1.09-1.24) and 'all asbestos-associated cancers' (SIR 1.27, 95% CI 1.14-1.42). The SIR for MM remained significantly increased when analyzed separately for males and females. Furthermore, the SIR for pharyngeal cancer in males was found significantly increased (SIR 1.69, 95% CI 1.22-2.33).

5.3 Study III

Cancer incidence ratios
We observed an increased incidence of MM (SIR 7.26, 95% CI 3.26-16.15) and cancer of the corpus uteri (SIR 1.29, 95% CI 1.01-1.66) compared with the reference cohort. In contrast, we observed fewer ovarian cancer cases than expected in the school cohort (SIR 0.72, 95% CI 0.52-1.01), albeit the difference was non-significant. For female cancers, we observed a numerical but not significant excess of cancer in external female genitals/vagina, other female genitals, and cervix uteri. The incidence of breast cancer was similar to that observed in the reference cohort (SIR 0.98, 95% CI 0.89-1.09).

Hazard ratios
The HRs for MM (HR 7.41, 95% CI 2.49-22.06) and cancer of the corpus uteri (HR 1.32, 95% CI 1.02-1.75) were statistically increased for those exposed to environmental asbestos after adjustment for occupational and familial occupational asbestos exposure. The risk of lung cancer was increased for those exposed to familial asbestos exposure (HR 1.23, 95% CI 1.06-1.43) and for those subject to own occupational asbestos exposure (HR 1.38, 95% 1.06-1.80). As expected, this difference persisted when adjusted for smoking (HR 3.55, 95% CI 3.05-4.15). Subjects exposed to occupational asbestos had a significantly increased HR for cancer in the cervix uteri. They also had a significantly lower HR for development of ovarian cancer.

Smoking

Using the diagnosis of COPD as a proxy for smoking, we found 355 (5.9%) female smokers in the school cohort and 2,249 (4.2%) female smokers in the reference cohort. When using the proxy in the Cox proportional hazard model, those who smoked had a significantly increased HR for lung cancer (HR 3.55, 95% CI 3.05-4.15). The HR was not increased for smokers in any of the female cancers.

6. DISCUSSION

6.1 Main findings in the light of other studies

6.1.1 Malignant mesothelioma

Environmental asbestos exposure in childhood

The increased risk of MM we found after environmental asbestos exposure in childhood was also found in Casale Monferrato, an Italian town with an asbestos-cement factory like in Aalborg[12]. A similar finding was reported from the asbestos mining town Wittenoom in Australia, where subjects exposed to blue asbestos in childhood had an increased risk of MM compared with the Western Australian population[70]. In a British population-based case-control study, the risk of MM was higher in subjects who were younger than 20 years at first exposure than in subjects aged 30 years or more[14]. However, those exposed before 30 years of age by living within one mile of a potential source (e.g. asbestos factory) had no increased OR[14].

For those only exposed to environmental asbestos, we would expect a male:female ratio close to one[10]. The male to female ratio for those exposed only to environmental asbestos was 1.2:1 in our study (6 men and 5 women). We cannot rule out that this male to female ratio might be influenced by residual confounding. However, in a study from Casale Monferrato, Magnani et al. reported the same male to female ratio (35 men and 29 women) for those not exposed to occupational or para-occupational asbestos[71]. A higher male to female ratio of 1:2.3 was reported in a study from the Italian national surveillance system on MM due to non-occupational asbestos exposure[72].

Spatial risk

In Paper I, no trend between school distance to the asbestos-cement factory and risk of MM was established. This is in contrast with results from other studies on spatial risk and mesothelioma[12,73-77]. In a study from Catalonia, Spain, the incidence rate of environmental pleural mesothelioma was higher in the population living within 500 m of a factory than in those living in a radius of 500-2000 m, and much higher than in those living at 2,000-10,0000 m. In a study from Casale Monferrato, Magnani et al. also found a spatial trend with increasing distance from the asbestos-cement factory[12].

In a study on women, Panou et al. found that a “hotspot” of 20 parishes near asbestos-emitting facilities in Northern Denmark had a higher incidence of MM than the general Danish female population[74]. The highest incidence density of mesothelioma was recorded in the parish where the asbestos-cement factory

in Aalborg was located[74]. The main reason for the lack of spatial risk trend may be that the risk of MM does not change significantly if you go to a school 100 m or 750 m away from the asbestos-cement factory. Children walk around in the neighborhood with or without their parents and thus experience an exposure that is most likely the same as that in the area around all the schools.

Latency

In a study examining the relationship between time since first exposure and risk of MM, Reid et al. found that the rate and risk of pleural MM increased until 45 years following first exposure[78]. In our study, we have no knowledge of time of first exposure to asbestos. However, in the lag time analysis, we found that the vast majority had developed MM more than 30 years after their 7th grade school attendance.

We found no significant difference in the median age at diagnosis between the two cohorts; nor did we find a significant difference in the median age at diagnosis between those in the school cohort exposed to environmental asbestos and those exposed to occupational asbestos. This might indicate that the environmental asbestos exposure has been substantial enough to cause MM; and for some of those exposed to occupational asbestos, it could be a reflection of brief occupational exposure (Table 4 in paper I). Alternatively, age at diagnosis does not depend on either level or time of exposure.

6.1.2 Cancers besides malignant mesothelioma

All cancers and all asbestos-associated cancers

An increased all cancer risk in cohorts exposed to occupational asbestos has been found in several studies[79,80]. In a cohort from Wittenoom exposed to environmental asbestos in childhood, both males and females also had an excess mortality from all cancers[70]. In our study, the additional analysis in Study II revealed that only males had a significantly increased risk of all cancers and all asbestos-associated cancers" which could be suggested to be associated with the greater asbestos exposure in males in the school cohort; more males had additional asbestos exposure from occupation or/and relatives (Table S1).

Multiple cancers

Few studies have investigated the influence of asbestos on developing multiple cancers, and most studies have described cases with multiple primary cancers and their association with potential asbestos exposure[81,82]. Bianchi et al. found co-existence of mesothelioma and other primary malignancies to be a relatively frequent event; 18.9% of cases had additional malignancies[83]. To

our knowledge, we are the first to examine the incidence of developing multiple primary cancers after environmental asbestos exposure. The incidence of multiple cancers in the school cohort was similar to that of the reference cohort, both in the overall school cohort, when divided into gender and when the cohort was divided into the asbestos exposure subgroups. Our results hence reject the hypothesis that environmental asbestos exposure in childhood increases the risk of developing multiple cancers.

Lung cancer

An increased lung cancer mortality has been found both among workers and residents in Wittenoom, Australia[84,85]. No increased lung cancer incidence or mortality was found in either men or women in the Wittenoom cohort exposed to environmental levels of crocidolite during childhood[70]. Nor did Camus et al. find any excess risk of death due to lung cancer among women in two chrysotile-asbestos-mining regions in Quebec compared with women in 60 control areas[86]. In Casale Monferrato, the population without occupational asbestos exposure had no increased mortality from lung cancer, but a large excess mortality was found among men and women exposed in asbestos-cement production. All these results are consistent with our findings. The SIR for cancer in the lung was significantly increased in the subgroup of former school children exposed both to environmental and occupational asbestos, which suggests that the overall increase in cancer of the lung may be due to occupational exposure, since no increased risk was observed in the other exposure subgroups.

Female cancers

Among the female cancers, the IARC has established a causal association only between asbestos exposure and ovarian cancer[1]. Women and girls exposed to environmental asbestos have been found to have a positive, though non-significant, increase in ovarian cancer incidence and mortality[46,85]. In contrast, Australian Blue Asbestos workers in Wittenoom had a lower risk of ovarian cancer, a result also found among women exposed to occupational asbestos in the school cohort [87].

In Casale Monferrato, women exposed to occupational asbestos showed a statistically significant increase in malignant neoplasm of the uterus[88]. In the group of women in the school cohort, only those exposed to environmental asbestos alone had a significantly higher HR for cancer of the corpus uteri. However, we found no increased risk for subjects with additional asbestos exposure from either occupation or from relatives. This might indicate that our finding is incidental. However, given the relative rarity of cancer in corpus uteri

and the low ratio of women exposed to occupational asbestos, the analysis may be more robust in the environmental/unknown group, and it could therefore be a true finding.

6.2 Methodological considerations

The main strengths of our study are the use of Danish high-quality registries, the large population, and the long follow-up period, which is important in respect of the long latency period. Using the register-based study design, we avoid recall bias, which could have constituted a potential problem because of the poorer recall in elderly cancer patients and the long time interval asked about. Although the data from Danish register are regarded valid, our findings might be skewed due to misclassification of a non-differential kind. This could tend to move the risk estimate towards zero.

6.2.1 Population and follow-up

From the school cohort, 796 subjects had attended more than one of the four schools. Due to divergent data in the school records, it was not possible to sum up time attended in each school. In all analyses, except the trend analysis, subjects from the school cohort have been counted as so regardless of which school they attended and for how long. Subjects from both cohorts were excluded from the analysis if they had been diagnosed with a cancer (except non-melanoma cancer) before entering the 7th grade. This was done to avoid bias; subjects surviving certain types of cancer are at increased risk of developing a second primary cancer[89]. In Paper II, we found that asbestos exposure does not increase the risk of developing more than one cancer. In Paper III, where all cancers were counted, this might cause an overestimation of the role of environmental asbestos exposure if there were any women in the school cohort who developed more than one cancer.

Had we started follow-up before the CPR number was introduced on 2 April 1968 (start of CRS), the cohort would only have consisted of “survivors”, resulting in selection survival bias, and a potential underestimation of a causal association could have been the result.

6.2.2 Asbestos exposure

Environmental asbestos exposure

The significantly higher risk of MM in the subgroup of school cohortees not exposed to either occupational asbestos or relatives’ occupational asbestos supports the hypothesis that children who attended school and lived near the asbestos-cement factory have been sufficiently asbestos exposed to have an increased risk of MM.

Our data do not provide us with a period for how long a subject has been exposed to environmental asbestos. In Paper I, we performed an additional analysis to examine the risk of MM for those 75.3% of the former school children who were born in a parish near the asbestos-cement factory, assuming that they had lived in the area for a longer period. This restricted cohort had a HR 5.99 (95% CI 3.59-10.01) compared with 7.15 (95% CI 4.54-11.27) in the entire school cohort. This may indicate that low-level environmental asbestos exposure in childhood, no matter how long, is enough to increase the risk of MM.

NOA does not exist in Denmark. However, NOA could be a potential confounder for subjects who have spent their childhood outside of Denmark in areas with NOA. Before the start of the CRS, we had no data on emigration or living addresses. Therefore we indirectly adjusted for NOA in a sensitivity analysis, restricting the analysis by excluding subjects not born in Denmark. This did not alter the HR significantly, and NOA was not considered a significant confounder in this study.

Occupational asbestos exposure

Using a register-based study design, we do not have asbestos exposure measurements on an individual level. In order to supply the study with occupational exposure data, we used individual information on occupational titles and linked it with the edited Danish NOCCA JEM. In the translation and evaluation of the Finnish O-codes, we discovered that some occupations were missing. These occupations were added to the JEM.

For MM, there is no evidence of a safe threshold level below which asbestos fibers cannot cause cancer[40]. Therefore, we did not consider quantifying the occupational asbestos exposure for Study I. However, for the other types of cancer, we did consider the use of 'mean level of exposure' in the evaluation of occupational asbestos exposure. Because of lack of quantitative information on the added occupations, we decided to use the same approach in Study II and III.

A critique of the use of JEMs has been that exposure data are presented as if they have been measured with a precision that cannot be scientifically justified[5]. Using only the proportion of exposed in dichotomizing subjects into ever/never exposed to occupational asbestos, we avoid using the historical level estimations, which are impossible to validate. Classification of those exposed to occupational asbestos according to the proportion of exposed within a job allowed for the best possible assessment of potential occupational asbestos exposure. A higher number of male cases with unknown asbestos

exposure may indicate that some expected misclassification from the use of the JEM has happened. However, the performed sensitivity analyses in Paper I did not reveal large changes in the results, which suggests that the misclassification is limited. Non-differential misclassification is unavoidable and may attenuate the hypothesized association between environmental asbestos exposure and development of cancer.

6.2.3 Confounding

Smoking is a great confounder for several cancer types[90]. In Study II, we found a significantly increased incidence of asbestos- and tobacco-associated cancers in the school cohort compared with the reference cohort. For lung cancer cases from both cohorts, the majority have been registered in the DLCR as former or current smokers. However, for the other cancer types, we have no data on smoking status, which limits the interpretation of a possible causal association and/or potential additive/multiplicative effect.
In Study III, we retrieved data on subjects diagnosed with COPD, which was used as a proxy for smoking. Since not all smokers will be diagnosed with COPD and not every COPD patient has a history of smoking, misclassification is unavoidable. However, the significantly increased HR for lung cancer in female smokers may indicate that COPD is suitable as a proxy for smoking.

Another important confounder is alcohol consumption. It has been established that alcohol consumption causes cancers of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast[90]. In the additional analyses in Study II, we observed an increased SIR for cancer of the pharynx in males. If alcohol consumption was a significant confounder, we would have expected increased SIRs for other cancer sites associated with alcohol consumption. We did not observe increased SIRs in other alcohol associated cancers.

We acknowledge that co-carcinogens and potential confounders such a smoking, alcohol consumption, and other lifestyle factors may have affected the incidence of certain cancers; the risk estimates associated with asbestos exposure might be higher than the true estimates. Due to the register based study design, data on these variables are not available wherefore our findings have inborn faults not fully accounted for.

7. CONCLUSION AND FUTURE PERSPECTIVES

The findings in this dissertation suggest that environmental asbestos exposure by school attendance near an asbestos-cement factory significantly increased the risk of certain types of cancer. Especially the incidence of MM was significantly increased among the former Aalborg school children, which confirms the strong association between environmental asbestos exposure and MM. We found the male incidence of 'all cancers' and 'all asbestos-associated cancer' was increased in the school cohort compared with the reference cohort. We also observed an increased risk of lung cancer in former school children who had also been exposed to occupational asbestos. As for the female cancers, we found an increased risk of cancer of the corpus uteri in the subgroup of the school cohort only exposed to environmental asbestos. Albeit our results are place-specific and time-specific, they may indicate the risk associated with environmental asbestos exposure in childhood elsewhere, where asbestos is still in use and where asbestos-cement factories are situated in populated areas.

Despite the evidence of the carcinogenicity of all asbestos types, including chrysotile, asbestos remains in use around the world. The estimated worldwide asbestos consumption has decreased though; from approximately 2 million tons in 2010 to nearly 1.4 million tons in 2016[91]. Even though the European Commission in 2005 decided to ban nearly all uses of asbestos, the risk of asbestos exposure is still present from releases of asbestos from asbestos-containing building materials and insulation in older buildings[92,93]. Damage and deterioration of asbestos-containing materials may present a risk for future exposure to asbestos. Although the risk of exposure from friable asbestos-containing products may be higher for asbestos removal workers, environmental asbestos exposure to the public also seems possible. In the Netherlands, as of 2024, the government has prohibited asbestos roofing, which is the largest remaining source of asbestos fibers. This means that owners of buildings that have asbestos roofing are required to remove it[94]. We call for further studies to investigate the environmental asbestos exposure from asbestos-containing products, which may be a rising problem, and further restrictions in the asbestos regulations should be considered.

Those diagnosed with MM in Denmark can claim financial compensation if they have been exposed to asbestos either by occupation or via relatives. Some of the MM cases in our study have only been exposed to environmental asbestos so they are not entitled to compensation. In contrast, in the

Netherlands, it is possible to apply for compensation if the asbestos exposure has been either work-related or non-work-related[95]. In France, the Social Security Law of 2000 created the fund of indemnification, which compensates all asbestos victims[96]. With the results from our study, we suggest considering altering the Danish compensation regulations, making it apply to all MM cases regardless of the type of exposure.

8. ENGLISH SUMMARY

Background
Asbestos has been declared a proven human carcinogen. Levels of occupational asbestos exposure have been documented to be particularly carcinogenic. Previous studies have also confirmed that environmental neighborhood exposure increases the risk of malignant mesothelioma (MM), the cancer most strongly associated with asbestos. In Denmark, the only asbestos-cement factory operated in the city of Aalborg in the period 1928-1988. Approximately 620,000 tons of asbestos (89% chrysotile) were imported during the years of operation. Children living near the asbestos factory were potentially exposed to airborne inhalable asbestos fibers.

Aim
To examine the risk of cancer after childhood environmental asbestos exposure from having lived near and attending primary school near the asbestos-cement factory in Aalborg, Denmark.

Materials and methods
We conducted a retrospective register-based cohort study using Danish national registers. Using historical school records, we identified former pupils (born 1940-1970) from four schools located at a 100-750 meter distance in the prevailing wind direction from the asbestos-cement factory in Aalborg. Our study included 12,111 former pupils (50.3% males and 49.7% females) and a reference cohort of 108,987 gender and five-year frequency-matched subjects. We evaluated, edited, and supplemented the Danish version of the NOCCA JEM to use it for adjustment for subjects' own occupational asbestos exposure and family members' occupational asbestos exposure. Data were analyzed using Cox proportional hazards (Study I and III) and by estimation of standardized incidence ratios.

Results
In Study I, the school cohort had a hazard ratio for MM of 7.15 (95% CI 4.54-11.27) adjusted for own occupational asbestos exposure and relatives' occupational asbestos exposure. No significant trend was established between school distance and risk of MM. In the school cohort, the male/female ratio was 1.2:1 for MM cases with no other known asbestos-assessed exposure than the environmental neighborhood exposure.
In Study II, the male incidence of 'all cancers', 'all asbestos-associated cancers', MM and pharyngeal cancer was increased in the school cohort compared with the reference cohort. The standardized incidence ratio (SIR)

of MM was significantly increased both for males and females in the school cohort. A significantly increased risk of cancer of lung cancer was found in the school cohort exposed to both environmental and occupational asbestos. We found no increased risk of developing multiple cancers in the school cohort compared with the reference cohort.
In Study III, we observed an increased risk of MM and cancer of the corpus uteri in females from the school cohort exposed to environmental asbestos. The risk of cancer of lung cancer was increased for those subjected to relatives' asbestos exposure or own occupational asbestos exposure and smokers. Furthermore, women exposed to occupational asbestos had a significantly increased hazard ratio for cancer in the cervix uteri, but a significantly lower risk of ovarian cancer.

Conclusion
An increased risk of MM and cancer of the corpus uteri in former school children suggests an effect of childhood environmental asbestos exposure. Our results show no indication of an increased risk of developing multiple cancers after environmental asbestos exposure in childhood.
In the light of our results, we suggest considerations be made towards altering the Danish compensation regulations, making it apply to all MM cases regardless of the type of exposure. Finally, we call for further studies to investigate the need for implementing further restrictions in the asbestos regulations.

9. DANISH SUMMARY

Baggrund

Asbest er kræftfremkaldende for mennesker. Tidligere studier har vist, at miljømæssig asbesteksponering i nærmiljøet øger risikoen for lungehindekræft, dén kræftform, der er tættest associeret med asbestudsættelse. I Danmark lå den eneste asbestcementproducerende fabrik i Aalborg, hvor den var i drift i perioden 1928-1988. Cirka 620.000 ton asbest (89% hvid asbest) blev importeret i produktionsperioden. Børn, der boede i nærheden af asbestfabrikken, kan potentielt have været eksponeret for asbestfibre i indåndingszonen.

Formål

At undersøge risikoen for kræft efter miljømæssig asbesteksponering i barndommen for personer, der gik i skole og boede i nærheden af asbestcementfabrikken i Aalborg, Danmark.

Materialer og metoder

Ved hjælp af nationale danske registre har vi gennemført et retrospektivt registerstudie. Vi fandt tidligere elever (født 1940-1970) ved at bruge historiske skoleindskrivningskort fra fire skoler, der lå i en afstand af 100-750 meter fra asbestcementfabrikken, alle i den dominerende vindretning. Studiet inkluderede 12.111 elever (50,3% mænd og 49,7% kvinder) og en referencekohorte bestående af 108.987 køn- og femårs-aldersfrekvens-matchede personer. Vi har evalueret, redigeret og suppleret den danske version af NOCCA jobeksponeringsmatricen for at bruge den til at justere for arbejdsmæssig asbesteksponering og familiemedlemmers arbejdsmæssige asbesteksponering. Data blev analyseret med Cox regressionsanalyser og ved at beregne standardiserede incidensrater.

Resultater

I studie I have skolekohorten en hazard-ratio for lungehindekræft på 7,15 (95% CI 4,54-11,27) justeret for egen arbejdsmæssig asbesteksponering og familiemedlemmers arbejdsmæssige asbesteksponering. Der fandtes ikke en signifikant trend mellem skoleafstanden til asbestfabrikken og risikoen for lungehindekræft. I skolekohorten var mand/kvinde-ratioen 1,2:1 for lungehindekræfttilfælde, som kun havde været miljømæssigt asbesteksponeret i nærmiljøet.

I studie II havde mændene i skolekohorten en øget incidens for alle cancere, alle asbestassocierede cancere herunder lungehindekræft og kræft i svælget

sammenlignet med referencekohorten. Den standardiserede incidensrate (SIR) for lungehindekræft var signifikant øget for både mænd og kvinder i skolekohorten. Vi fandt en signifikant øget risiko for at få lungekræft for dem i skolekohorten, der var udsat for både miljømæssig og arbejdsmæssig asbest. For personer i skolekohorten fandt vi ikke en øget risiko for at udvikle flere cancere i forhold til referencekohorten.

I studie III observerede vi en øget risiko for lungehindekræft og kræft i livmoderen for piger i skolekohorten, der kun havde været miljømæssigt asbesteksponeret. Risikoen for at få lungekræft var øget for rygere og for dem, der havde familiemedlemmer, der var arbejdsmæssigt asbesteksponeret, eller hvis de selv havde været arbejdsmæssigt asbesteksponerede. Desuden havde kvinder, der havde været arbejdsmæssigt asbesteksponeret, en signifikant øget hazard-ratio for livmoderhalskræft, men en signifikant lavere risiko for æggestokkekræft.

Konklusion
En øget risiko for lungehindekræft og livmoderkræft hos de tidligere skoleelever tyder på, at der er en effekt af miljømæssig asbestudsættelse i barndommen. Vores resultater viser ikke tegn på en øget risiko for at udvikle flere cancere efter miljømæssig asbestudsættelse i barndommen. På baggrund af vores resultater foreslår vi, at man overvejer en ændring i de danske erstatningsregler, så de gælder for alle med lungehindekræft, uanset hvordan de er blevet eksponeret. Endelig opfordrer vi til flere studier, der skal undersøge, om der er behov for at indføre yderligere begrænsninger i asbestbekendtgørelsen.

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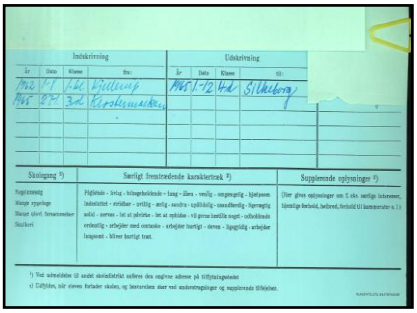
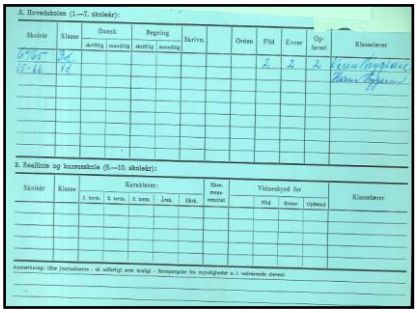
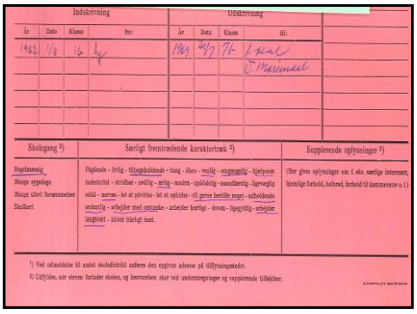
12. SUPPLEMENTARY DOCUMENTS

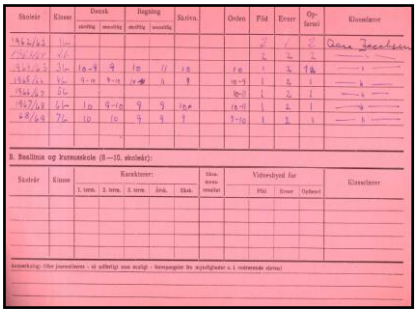
12.1 School records

School records provided by the Aalborg City Archive; blue records for boys and pink records for girls. The school records contain personal information, data on enrolment, name of school, years attended, and grades.









12.2 Danish industries with potential asbestos exposure

DSE77 code	Industries with potential asbestos exposure
71110	Railroads
71162	Rescue squads
71163	Fire brigade
91032	Marine
37102	Iron foundries
37200	Metal works and foundries
37201	Metal works
37202	Metal foundries
38000	Iron and metal industry
38100	Iron and metal goods industry
39010	Manufacture of gold and silver articles
38412	Wooden shipyards and boat builders
38419	Manufacture of other ship equipment
38420	Manufacture of railroad equipment
38411	Iron shipyards
38413	Marine engine manufacture
38431	Manufacture of automobiles
50160	Plumbing businesses
50170	Electrical contracting firms
33114	Manufacture of building articles
50140	Building and carpentry firms
35210	Paint and varnish factories
38196	Industrial painting
39097	Sign factories and sign painters
50150	Painting firms
50199	Other building activities
50192	Insulation firms
50121	General contracting businesses
50195	Stove installation
95100	Repair of automobile, household equipment, etc.
95130	Auto repair, etc.
95131	Auto repair shops
92023	Chimney sweeps

12.3 Table 1 in Paper II presented separately for ♂ and ♀

Table S1 Characteristics of the Aalborg School Children Cohort and the sex and age-matched reference cohort.

	School cohort (n=12,111)		**Reference cohort (n=108,987)**	
	♂	♀	♂	♀
Characteristics	**n (%/range)**	**n (%/range)**	**n (%/range)**	**n (%/range)**
Sex	6,087	6,024	54,787	54,200
Birth-year				
1940-1944	1,219 (20.0)	1,190 (19.8)	10,980 (20.0)	10,707 (19.8)
1945-1949	1,509 (24.8)	1,452 (24.1)	13,578 (24.8)	13,067 (24.1)
1950-1954	1,336 (22.0)	1,335 (22.2)	12,021 (21.9)	12,008 (22.1)
1955-1959	1,095 (18.0)	1,071 (17.8)	9,853 (18.0)	9,645 (17.8)
1960-1964	697 (11.5)	754 (12.5)	6,269 (11.4)	6,778 (12.5)
1965-1970	231 (3.8)	222 (3.7)	2,086 (3.8)	1,995 (3.7)
Person-years of follow-up	295,349	297,637	2,547,401	2,583,877
Median attained age	62.1 (13.5-76.0)	63.0 (14.8-76.0)	61.3 (12.3-76.0)	62.2 (12.0-76.0)
Type of asbestos exposure				
Only environmental asbestos exposure/ No known asbestos exposure	3,668 (60.3))	4,345 (72.1)	40,496 (73.9)	43,029 (79.4)
Occupational asbestos exposure	1,623 (26.7)	138 (2.3)	8,479 (15.5)	1,206 (2.2)
Relatives' occupational asbestos exposure	501 (8.2)	1,415 (23.5)	2,645 (4.83)	7,753 (14.3)
Occupational and familial occupational asbestos exposure	207 (3.4)	80 (1.3)	789 (1.4)	414 (0.76)
No Supplementary Pension Fund Register data	88 (1.5)	46 (0.76)	2,378 (4.3)	1,798 (3.3)

12.4 Table 2 in Paper II presented separately for ♂ and ♀

Table S2 Standardized incidence ratios (SIR) for cancer (1968-2015) among 12,111 former school children from Aalborg

	Observed number of cases					
	School		**Reference**		**SIR (95% CI)**	**SIR (95% CI)**
Cancer site	♂	♀	♂	♀	♂	♀
All cancers * (minus non-melanoma skin cancers)	915	912	6,828	7,991	**1.17 (1.09-1.24)**	0.99 (0.93-1.06)
All asbestos-associated cancers *	325	255	2230	2211	**1.27 (1.14-1.42)**	1.00 (0.89-1.14)
Colon	67	52	500	477	1.17 (0.92-1.49)	0.94 (0.72-1.24)
Larynx	21	4	124	25	1.47 (0.96-2.26)	1.37 (0.52-3.66)
Lung	115	121	911	942	1.10 (0.92-1.32)	1.11 (0.93-1.33)
Malignant mesothelioma	32	6	31	7	**9.13 (6.46-12.91)**	**7.36 (3.30-16.37)**
Ovary	-	33	-	403	-	**0.71 (0.50-0.99)**
Pharynx	37	3	188	71	**1.69 (1.22-2.33)**	0.36 (0.12-1.11)
Rectum	40	27	356	251	0.99 (0.72-1.34)	0.94 (0.65-1.37)
Stomach	21	12	175	73	1.04 (0.68-1.60)	1.44 (0.82-2.54)
Multiple cancers (>1 cancer)	67	88	587	676	1.01 (0.79-1.28)	0.96 (0.78-1.18)

*Individuals with at least one cancer.
Bold denotes statistically significant results, p<0.05

13. PAPERS I-III

I. Environmental asbestos exposure in childhood and risk of mesothelioma later in life: a long-term follow-up register-based cohort study [Accepted for publication in Occup Environ Med]

II. Cancer incidence and risk of multiple cancers after environmental asbestos exposure in childhood - a long-term register-based cohort study [Manuscript]

III. A cohort study on cancer incidence among women exposed to environmental asbestos in childhood with focus on female cancers including breast cancer [Manuscript]

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